Alerts, Notices, and Case Reports

Monoamine Oxidase Inhibitor Overdose

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THE MANAGEMENT OF patients who have overdosed with nonselective, irreversible monoamine oxidase inhibitors (MAOIs) is an infrequent but recurring challenge in most medical centers. Being infrequent, such cases of overdose often catch physicians off guard. The ability to anticipate overdose complications provides the best chance of guiding patients to successful outcomes.

Monoamine oxidase inhibitors were noted to alleviate depression in Swiss sanitariums in patients with tuberculosis who were receiving isoniazid, an antituberculous MAOI.[1] Similarly, in 1958 the use of iproniazid was reported in the treatment of depressive illness.[2] Although they are often not considered first-line therapy for depression, MAOIs are still used, particularly in cases involving comorbid anxiety, atypical depression associated with hypersomnia, insomnia, panic attacks, and bulimia.[3]

The often-feared interactions associated with MAOI use probably discourage wider use. Overdose with the use of MAOIs carries a risk of death that is not trivial. The case described herein illustrates some of the problems occurring from overdose with an MAOI and the need for close consultation with skilled toxicology professionals.

Report of a Case

The patient, a 36-year-old married homemaker with an eight-year history of depression and multiple personality disorder, presented to the emergency department between two and four hours after ingesting approximately 140 10-mg tranylcypromine sulfate tablets during a period of modest family stress. Eight years before this event she had attempted suicide with a clonazepam overdose.

The patient had been on a regimen of clonazepam, 1 mg three times a day with an added dose of 3 mg at night, and tranylcypromine, 60 mg once a day. An hour before admission she had awakened her husband, told him of the ingestion, and induced emesis that included pill fragments. She said she did not use alcohol, but reported that she had been taking an unknown over-the-counter cold medicine for a few days before admission.

In the emergency department, the patient was alert and oriented. Her vital signs were stable; she had a dry oral mucosa, her pupils were dilated to 5 mm, and her skin was warm and dry. Her initial chemistry values, blood count, and chest x-ray film revealed no abnormalities. An electrocardiogram showed sinus tachycardia. The patient was transferred to the intensive care unit.

Four hours after admission the patient became agitated, had difficulty following commands, urinary retention developed, and she began to thrash her arms about. She was given 2 mg of diazepam in an effort to alleviate these symptoms. Over the next few hours the patient's agitation worsened, and a temperature of 38.5°C (101.3°F) developed. During the eighth hour after admission, in an effort to protect the patient from hyperthermia and rhabdomyolysis and to improve behavior control, a lorazepam drip was started and the dosage gradually increased over the ensuing hour to a rate of 80 mg an hour.

During the tenth hour after admission, despite the administration of high doses of benzodiazepines, acetaminophen, and a cooling blanket, the patient continued to have psychomotor agitation and hyperpyrexia. Uncertain whether seizure activity was developing, the patient was given a loading dose of 800 mg of phenobarbital over an hour, and a continuous drip of 60 mg every 20 minutes was started. The patient's airway was protected with a nasal trumpet and oxygen administered through a nasal cannula.

In the 16th hour after admission, the patient had a tonic-clonic seizure lasting about five minutes. A blood phenobarbital concentration was within the therapeutic range. A midazolam maleate drip was subsequently begun to further decrease any residual psychomotor agitation. After the seizure, the large doses of benzodiazepines required to control psychomotor agitation led to the need for mechanical ventilation. The patient was given 28 mg of atracurium mesylate and a nasotracheal tube inserted. Because of lorazepam's long half-life, the lorazepam drip was stopped. The midazolam dosage was titrated to eradicate psychomotor agitation and reached a maximum of 90 mg an hour; 48 hours after admission, the midazolam drip was gradually discontinued, the phenobarbital stopped, and the patient's nasotracheal tube removed. She was then transferred to a psychiatric ward.

Throughout her hospital stay, the patient displayed agitation, tremulousness, hyperpyrexia, and seizure, which are typical signs of MAOI toxicity. She did not have hypertension or flushing, which are also common signs.

Discussion

Monoamine oxidase inhibitors block the body's ability to oxidatively deaminate naturally occurring monoamines both in the central nervous system (CNS) and the periphery. As with tricyclic antidepressants and serotonin reuptake inhibitors, it is postulated that the increase in CNS intrasynaptic monoamines such as norepinephrine and serotonin impart a reequilibrium on postreceptor expression that over a period of time leads to an antidepressant effect.

(Thorp M, Toombs D, Harmon B. Monoamine oxidase inhibitor overdose. West J Med 1997 Apr; 166:275–277)

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ABBREVIATIONS USED IN TEXT
CNS = central nervous system
MAOI = monoamine oxidase inhibitor

The difficulty in using MAOIs is their possible interactions with other drugs or food substances or in pure overdose of the MAOI itself. As listed in Table 1, a wide range of drugs interact with MAOIs. In Table 1 is also included generalizations about the pharmacology of the more common and severe interactions involving the use of MAOIs and the metabolism of general anesthetics, sedatives, antihistamines, alcohol, and antidepressants such as imipramine hydrochloride and amitriptyline hydrochloride, the effects of which may be prolonged and intensified.[4] Beyond inhibiting the metabolism of other drugs, MAOIs cause a buildup of adrenergic neurotransmitters in peripheral neuronal tissue that can lead to severe interactions with indirect-acting sympathomimetics. Ephedrine, pseudoephedrine, phenylpropanolamine, and tyramine are

TABLE 1.—*Adverse Monoamine Oxidase Inhibitor (MAOI) Drug Interactions**

Drug	*Effect of Interaction*
Amphetamines, Buspirone, Dextromethorphan, Dopamine, Ephedrine, Levodopa, Norepinephrine (formerly levarterenol) bitartrate, Mephentermine sulfate, Metaraminol bitartrate, Methylphenidate HCl, Phenylephrine HCl, Phenylpropanolamine bitartrate, Procaine HCl (dissolved in epinephrine), Pseudoephedrine	All increase blood pressure†
Aspartame	Headache and diaphoresis with phenelzine sulfate‡
Fluoxetine	Serotonergic syndrome requiring 5-week interval between discontinuation of fluoxetine and start of MAOI†
Heterocyclic antidepressants	Hyperpyrexia, excitability, muscular rigidity, convulsions, and coma with abrupt switch between MAOIs and heterocyclic agents†; inhibit metabolism, increasing heterocyclic antidepressant blood levels and toxicity†; increased incidence of mania§; disseminated intravascular coagulation with clomipramine HCl‡
Meperidine HCl	Excitation, sweating, fever, rigidity, hyperreflexia, hypertension, and delirium—can be life-threatening‖
Succinylcholine chloride	Phenelzine may prolong apnea†
Anticholinergics, barbiturates	All may enhance central nervous system depression§
Codeine, general anesthetics, propoxyphene HCl and napsylate	Labile blood pressure with atracurium besylate‡
Benzodiazepines	Disinhibition and generalized edema with chlordiazepoxide§
Insulin	Increased incidence of hypoglycemic episodes†
Sulfonylureas	Increase hypotension§
Antipsychotics, reserpine, and thiazide diuretics	All increase hypotension§; increased extrapyramidal signs with phenylthiazines§; catatonia with haloperidol and phenelzine sulfate‡; frank mania with reserpine and nialamide‡
Guanethidine monosulfate	Decreased antihypertensive effect§
Methyldopa	Excitation and hallucinations with pargyline HCl‡
Alcohol	May induce severe hypertension†; increased central nervous system depression§; malignant hyperthermia‡
MAOIs	Hyperpyrexia, hypertension, and hyperreflexia with abrupt switch from phenelzine to tranylcypromine‖
Sulfisoxazole	Ataxia and paresthesias‡
Bupropion HCl	Enhanced acute toxicity with phenelzine#
Amantadine HCl	Elevated blood pressure‡
Lithium carbonate or citrate	Tardive dyskinesia with tranylcypromine§

HCl = hydrochloride

*From Hardman et al.[3] †Substantial interaction. ‡Mild interaction or single case. §Potentially serious interaction. ‖Severe interaction. #Not clinically important.

taken up by sympathetic neurons and cause the release of norepinephrine in supranormal amounts in nerve endings. This can lead to a severe adrenergic response, one of the most predominant being severe hypertension.[5] A third mechanism of interaction involves drugs that inhibit the reuptake of serotonin such as tricyclic antidepressants, serotonin reuptake inhibitors, meperidine hydrochloride, and dextromethorphan. The MAOI interaction with these drugs has been called "the serotonin syndrome" and manifests as restlessness, tremor, and monoclonus as a prelude to seizures and coma. The syndrome is thought to be caused by the combination of decreased serotonin degradation and the inhibition of reuptake.[6]

In cases of the overdose of MAOIs, symptoms include hypertension, tachycardia, flushing, tachypnea, pulmonary edema, hyperpyrexia, agitation, drowsiness, headache, seizures, and coma.[7] Of note is that profound hypotension, bradycardia, cardiovascular collapse, and asystolic arrest may follow the overdose of MAOIs alone.[8] If the treatment of hypotension is refractory to fluid replacement or other nonpharmacologic means, direct-acting sympathomimetics such as norepinephrine or dopamine may be used cautiously. This is because they are metabolized primarily by catechol *O*-methyltransferase and do not require the release of intracellular amines.[9]

The evaluation of a case of MAOI overdose should include a history of additional drug use such as sympathomimetic agents. It is important to recognize, however, that tranylcypromine and selegiline hydrochloride are metabolized to amphetamine-like structures and can be reported as such on toxicologic screens.[10] Our patient's positive toxicology screen for amphetamines was available within the first few hours, but given the confounding tranylcypromine metabolite, this information was of minimal usefulness.

This patient had numerous side effects that have been documented with MAOI overdose: hyperthermia that required the administration of acetaminophen and a cooling blanket, agitation that required large doses of lorazepam, and then seizures that required paralysis and intubation. Severe hypertension did not develop (for which nifedipine might have been used), nor did hypotension, bradycardia, cardiovascular collapse, or cardiac arrest. There was no evidence of the use of a serotonin reuptake inhibitor. Her toxicologic screen was positive for benzodiazepines—the patient was taking clonazepam—and amphetamines. Although the clonazepam may have played a role in the patient's respiratory depression,[11] the large quantities of midazolam and diazepam required for sedation were probably more substantial. The patient had taken an unknown over-the-counter cold medication that could have been the cause of the amphetamines in the toxicology screen. As stated earlier, tranylcypromine is metabolized to amphetamine-like structures, which could also account for these positive findings.

The treatment of patients with severe personality disorders is difficult and often fraught with risks, including overdose. Efforts are being made to produce more specific MAOIs, targeting enzyme subsets located primarily in the CNS.[12] Although it is hoped that such medications will provide patients the antidepressant effects of MAOIs without the grave risks of interactions, current information remains mixed.[13] With these new medications, the use of MAOIs may show a resurgence. Until then, the danger of interactions and overdose will continue to overshadow the use of these agents.

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Eosinophilic Tuberculous Pleural Effusion

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PLEURAL FLUID EOSINOPHILIA is defined as greater than 10% eosinophils in the pleural leukocyte differential count, and as many as 8% of cases of exudative pleural effusions are eosinophilic.[1] The most common conditions associated with eosinophilic pleural effusions are previous thoracen-

(Bassiri AG, Morris W, Kirsch CM. Eosinophilic tuberculous pleural effusion. West J Med 1997 Apr; 166:277–279)

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